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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/701,014	11/22/2000	Kyriacos A. Mitraphanous	550 184	4760

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EXAMINER
GUZO, DAVID

ART UNIT	PAPER NUMBER
1636	7

DATE MAILED: 07/08/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/701,014	Applicant(s) MITRAPHANOUS ET AL.	
	Examiner David Guzo	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

It is noted that this application appears to claim subject matter disclosed in prior copending Application No. 60/093,149, filed 7/17/98 and PCT/GB99/01607, filed 5/21/99. A reference to the prior application must be inserted as the first sentence of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). Also, the current status of all nonprovisional parent applications referenced should be included.

If the application is a utility or plant application filed on or after November 29, 2000, any claim for priority must be made during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2) and (a)(5). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) a surcharge under 37 CFR 1.17(t), and (2) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Commissioner may require additional information where there is a question whether the delay was unintentional. The petition should be directed to the Office of petitions, Box DAC, Assistant Commissioner for Patents, Washington, DC 20231.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant claims a pharmaceutical composition comprising a retroviral vector delivery system derived from EIAV, MLV or HIV wherein the retroviral vector is pseudotyped with rabies G

protein or a mutant, variant or derivative thereof. The retroviral delivery system is contemplated for use in a gene therapy method of treating a patient.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (See *United States v. Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). These factors include the following:

1) Unpredictability of the art. The gene therapy art is extremely unpredictable. This unpredictability is manifested at practically every level of gene therapy, from the design of the vector, manufacture of the vector, delivery of the vector to the proper target cells or tissues *in vivo*, transient or inefficient expression of the transgene in cells *in vivo*, etc. Specifically, with regard to RNA vectors such as retroviral vectors, the silencing of transgene expression has been postulated to be due to methylation in the vicinity of the promoter and/or incorporation of the insertion site into condensed chromatin, in which the transgene is inaccessible to the cell's transcription machinery. With regard to lentiviral vectors, no clinical experience has been accumulated and their ability to function as gene therapy vectors in humans is unknown. For reviews of the gene therapy art, see Anderson, Nature, Vol. 392, 1998, pp. 25-30; Verma et al.,

Nature, Vol. 389, 1997, pp. 239-242; Mountain, TIBTECH, Vol. 18, 2000, pp. 119-128; Kmiec, American Scientist, Vol. 87, 1999, pp. 240-247, etc.).

2) State of the art. The art at the time of applicant's invention was nil, with no demonstrated unambiguous successes in treating any disease in humans. With regard to lentiviral vectors, no clinical experience has been accumulated.

3) Number of working examples. Applicant presents no working examples of the claimed invention.

4) Amount of guidance presented in the specification. Applicant presents no guidance on how the skilled artisan would practice successful gene therapy using the claimed rabies G protein pseudotyped retroviral vectors. Applicant presents no guidance on how the skilled artisan would address and overcome the art recognized problems associated with successful practicing of gene therapy in patients.

5) Scope of the claims. The claims are broad with the claims reciting a pharmaceutical composition comprising the rabies G protein retroviral delivery system for the treatment of any disease.

6) Nature of the invention. The invention involves one of the most complex and unpredictable areas of medicine/molecular biology; gene therapy.

7) Level of skill in the art. The level of skill in the gene therapy art is high; however, as noted by some of the preeminent researchers in gene therapy (i.e. W. French Anderson, I. M. Verma, etc.),

significant hurdles remain to be overcome in order for the skilled artisan to practice successful gene therapy.

Given the above analysis of the factors which the courts have determined are critical in ascertaining whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to have conducted undue and excessive experimentation in order to practice the claimed invention.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-4, 6-11, 13-20 are rejected under 35 U.S.C. 102(e) as being anticipated by Bremel et al. (U.S. Patent 6,080,912).

Applicants claim a retroviral delivery system comprising a retroviral vector pseudotyped with the rabies G protein. The retroviral vector can be derived from lentiviruses such as HIV or viruses such as MLV and comprises a sequence encoding a protein of interest (which can be a

protein with some therapeutic potential) wherein said vector is capable of transducing dividing and non-dividing cells. Applicants also claim a cell transduced with said retroviral vector and methods of delivering a nucleotide sequence of interest to a target cell comprising contacting the cell with the vector and methods of using rabies G protein to alter the host ranges of retroviruses or retroviral vectors.

Bremel et al. (See whole document, particularly claims 5 and 12-14, columns 6-10) discloses a retroviral delivery system comprising a retroviral vector which can be pseudotyped with the rabies G protein (so as to alter the host range of the virus). The retroviral vector to be pseudotyped can be a lentivirus such as HIV or a virus such as MLV and said vector can comprises a sequence encoding a protein of interest (which can be therapeutic) and wherein said vector can transduce dividing and non-dividing cells as a property of it's altered host range. Bremel et al. also discloses cells transduced with the vectors, methods of delivering a nucleotide sequence encoding a protein of interest to target cells and methods of altering the host range of retrovirus vectors by incorporating rabies G protein as the viral env protein. Bremel et al. therefore teaches the claimed invention.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made

to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bremel et al. In view of Olsen.

Applicants claim a retroviral delivery system comprising a EIAV vector pseudotyped with a rabies G protein.

Bremel et al. is cited as in the above 35 USC 102 rejection. While Bremel et al. teaches the generation of a variety of different retroviruses pseudotyped with rabies G protein, Bremel et al. does not teach the generation of EIAV vectors pseudotyped with rabies G protein.

Olsen (U.S. Patent 6,277,633, issued 8/21/01, effective filing date of 5/13/97, see whole document, particularly claims 1 and 7, columns 8-9) recites the use of heterologous envelope genes (such as VSV G protein) to expand the host range of EIAV vectors.

The ordinary skilled artisan, seeking to generate EIAV vectors pseudotyped with rabies G protein would have been motivated to combine the teachings of Bremel et al. on the generation of retroviral vectors pseudotyped with rabies G protein so as to expand the host range of the vectors with the teachings of Olsen on the use of heterologous env genes (such as VSV G

protein) to expand the host range of EIAV vectors in order to pseudotype EIAV vectors with the rabies G protein because Bremel et al. teaches that G proteins from rhabdoviruses such as VSV and rabies can be used to expand the host ranges of retrovirus vectors and Olsen teaches that EIAV can be likewise modified by incorporating a heterologous envelope protein (such as VSV G) to increase the host range of the EIAV. It would have been obvious for the ordinary skilled artisan to do this because both Bremel et al. and Olsen both teach the desirability of increasing the host range of retroviral vectors by incorporating a G protein from rhabdoviruses such as rabies or VSV into the envelopes of retrovirus vectors. Given the teachings of the cited prior art and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

> 35 U.S.C. 101 reads as follows:
> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 11 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claim 11 recites a cell transduced with the claimed retroviral delivery system. The cell can be *in vivo* in a human since a contemplated use of the retroviral delivery system is to deliver nucleotide sequences of interest to target cells in *vivo* as part of a treatment regime. If the claim is read as a transduced cell *in vivo*, the cell is part of a human being and the claim can be read as

claiming a part of a human or the human comprising the transduced cell. Claims reading on humans or humans comprising transduced cells are non-statutory.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (and dependent claims) are vague in the recitation of the phrase "...retroviral delivery system is derivable from..." MLV, HIV, EIAV, a lentivirus or oncoretrovirus. It is unclear how closely related to the starting virus the retroviral delivery system derived therefrom can be. Does the retroviral delivery system need to have a backbone sequence from one of the recited retroviruses or does the retroviral delivery system only need to have a portion of a sequence encoding some protein from one of the recited viruses? The metes and bounds of the claimed subject matter are unknown. Claims 1 and 3-5 are also vague in the recitation of sequences "...derivable from a retrovirus..." or derivable from a "...lentivirus or oncoretrovirus..." or derivable from a "...EIAV..." because it is unclear how closely related to the starting materials the derivatives can be. For example, if the sequence has one nucleotide of the sequence from the

original retrovirus from which it is derived, does this fall within the definition? The metes and bounds of the claimed subject matter are unclear.

Claims 6, 7 and 13 are vague in that the term "NOI" has not been defined in the claim.

Claim 10 is vague in the recitation of the phrase "...according to any one of claims 1..." because this claim language was not changed when the multiple dependency of the claim was changed by preliminary amendment.

Claim 11 is vague in the recitation of a cell transduced with the instant retroviral delivery system. The claim reads on a transduced cell *in vivo*. Since the transduced cell *in vivo* is not isolated but is a part of the human or animal it is unclear what applicants are claiming, the cell or the animal (human) comprising the cell.

Claim 14 is vague because the preamble of the claim merely recites "A method" without indicating what purpose the method is intended to accomplish.

Claim 15-16 provides for the use of a rabies G protein for pseudotyping a retrovirus, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 15-16 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for

example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim 20 is vague because there is no antecedent basis in claim 1 for the terms "pseudotyped retrovirus" or Retroviral vector" or "retroviral particle".

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo whose telephone number is (703) 308-1906. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242 or (703) 305-3014. Faxes may be sent directly to the examiner at (703) 746-5061.

Any inquiry of a general nature or relating to the status of this application or proceeding or relating to attachments to this Office Action should be directed to Patent Analyst Zeta Adams whose telephone number is (703) 305-3291.

DAVID GUZO
PRIMARY EXAMINER

David Guzo
July 3, 2002